Cutaneous Safety and Tolerability of a Fixed Combination Clindamycin (1.2%) and Benzoyl Peroxide (3.75%) Aqueous Gel in Moderate-to-severe Acne Vulgaris

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ABSTRACT

Objective: To investigate the cutaneous safety and tolerability of clindamycin phosphate 1.2%/benzoyl peroxide 3.75% gel in moderate-to-severe acne patients. **Methods:** A safety assessment of 498 patients with moderate-to-severe acne receiving clindamycin phosphate 1.2%/benzoyl peroxide 3.75% gel or vehicle for 12 weeks. **Results:** The vast majority (80–95%) of patients reported no cutaneous safety or tolerability problems throughout the study. Mean scores for both active and vehicle were all <1 (where 1=mild) and reduced over the duration of the study. When scaling, erythema, itching, burning, or stinging was reported it was generally mild. Moderate or severe reactions to clindamycin phosphate 1.2%/benzoyl peroxide 3.75% gel were rare and generally seen early in treatment. There were eight reports (3.3%) of moderate erythema, four reports (1.7%) of moderate scaling, three reports (1.2%) of moderate itching, and one report of moderate burning (0.4%) at Week 4. There was one report (0.4%) of severe erythema and one report (0.4%) of severe burning (both at Week 4), with one report (0.4%) of severe stinging at Week 12. There were no substantive differences seen in cutaneous tolerability among treatment groups and younger patients tended to have milder reactions. **Limitations:** It is not possible to determine the contributions of the individual active ingredients. **Conclusion:** Clindamycin phosphate 1.2%/benzoyl peroxide 3.75% gel has a favorable safety and tolerability profile with very low incidence of moderate or severe reactions.
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The treatment of a chronic disease, such as acne, is a long-term process complicated by adolescent patients' tendency for poor treatment adherence.[1–3] Typically, moderate acne will improve in 20 to 40 percent of patients within 12 weeks, and 50 percent or better by Week 26.[4] Compliance has been reported as low as 45 percent for daily application of topical antimicrobial acne treatments.[5] Indeed it has been suggested that poor adherence may be the most important factor in the failure of acne treatment.[6]

Cutaneous safety and tolerability of topical medications is a key determinant in patient adherence; however, good data on the association between tolerability and adherence is lacking.[7] One study that did find an association showed that patients treated with an adapalene/benzoyl peroxide (BP) 2.5% fixed combination missed more doses as a result of irritation and adverse events than with a less irritating clindamycin/BP 5% fixed combination product.[8]

How much patients are bothered by dryness and irritation from topical acne treatments and what action they take as a result is not well-characterized. It is well known that a potential limitation of BP is concentration-dependent irritation.[9] An internet-based survey of patients using clindamycin/BP 5% showed bothersome side effects, such as dry skin, flaky/peeling skin, irritation, itchiness, and redness to be very common, having a number of impacts on treatment patterns.[10] It was noted that to combat irritation, patients would often resort to treating spots only, using the product only when

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breakouts seemed worse, using the product sporadically, or switching to an over-the-counter product.[10] Topical retinoids are also potentially irritating to the skin, with dryness, erythema, stinging, and pruritus being common, especially over the first few weeks of therapy.[11]

Combining multiple therapies that are all potentially irritating can be a challenge. However, advances in formulation research, including the removal of potentially irritating surfactants, preservatives, alcohol, and parabens has lead to the introduction of fixed combinations with favorable cutaneous safety and tolerability profiles.[12] Recently, efficacy and tolerability data on a new fixed combination product, clindamycin phosphate 1.2%/BP 3.75% gel was reported.[13] In this paper, the cutaneous safety and tolerability is looked in greater detail, both in the overall population and outliers.

METHODS

Detailed methodology has already been reported elsewhere[13]; however, a summary is provided below.

Study design. A total of 498 patients with moderate-to-severe acne vulgaris were randomized (1:1) to receive clindamycin phosphate 1.2%/BP 3.75% gel or vehicle in a multicenter, double-blind, controlled, 12-week study. Patients were stratified by severity of acne (Evaluator's Global Severity Score [EGSS], ranging from 0 [clear] to 5 [very severe]). They were dichotomized into a moderate (EGSS of 3) and a severe (EGSS of 4) acne group.

Study population. Patients were included of any race or ethnicity with moderate-to-severe acne, defined as 20 to 40 inflammatory lesions (papules, pustules, and nodules), 20 to 100 noninflammatory lesions (open and closed comedones), and no more than two nodules. Standard washout periods were required for patients using previous prescription and over-the-counter acne treatments.

Safety evaluation. Safety endpoints included investigator assessments of cutaneous safety (scaling and erythema) and subject assessments of cutaneous tolerability (itching, burning, and stinging).

Cutaneous safety and tolerability evaluation scores were presented with descriptive statistics at baseline and at Weeks 4, 8, and 12 for each study drug group, on a scale of 0 (none) to 3 (severe)

TABLE 1. Cutaneous safety and tolerability evaluation scales

SCALING ASSESSMENT		
Score	**Grade**	**Description**
0	None	No scaling
1	Mild	Barely perceptible, fine scales present on limited areas of the face
2	Moderate	Fine scale generalized to all areas of the face
3	Severe	Scaling and peeling of skin over all areas of the face
ERYTHEMA ASSESSMENT		
Score	**Grade**	**Description**
0	None	No evidence of erythema present
1	Mild	Slight pink coloration
2	Moderate	Definite redness
3	Severe	Marked erythema, bright red to dusky dark red in color
ITCHING ASSESSMENT		
Score	**Grade**	**Description**
0	None	No itching
1	Mild	Slight itching, not really bothersome
2	Moderate	Definite itching that is somewhat bothersome
3	Severe	Intense itching that may interrupt daily activities and/or sleep
BURNING ASSESSMENT		
Score	**Grade**	**Description**
0	None	No burning
1	Mild	Slight burning sensation, not really bothersome
2	Moderate	Definite warm, burning sensation that is somewhat bothersome
3	Severe	Hot burning sensation that causes definite discomfort and may interrupt daily activities and/or sleep
STINGING ASSESSMENT		
Score	**Grade**	**Description**
0	None	No stinging
1	Mild	Slight stinging sensation, not really bothersome
2	Moderate	Definite stinging sensation that is somewhat bothersome
3	Severe	Stinging sensation that causes definite discomfort and may interrupt daily activities and/or sleep

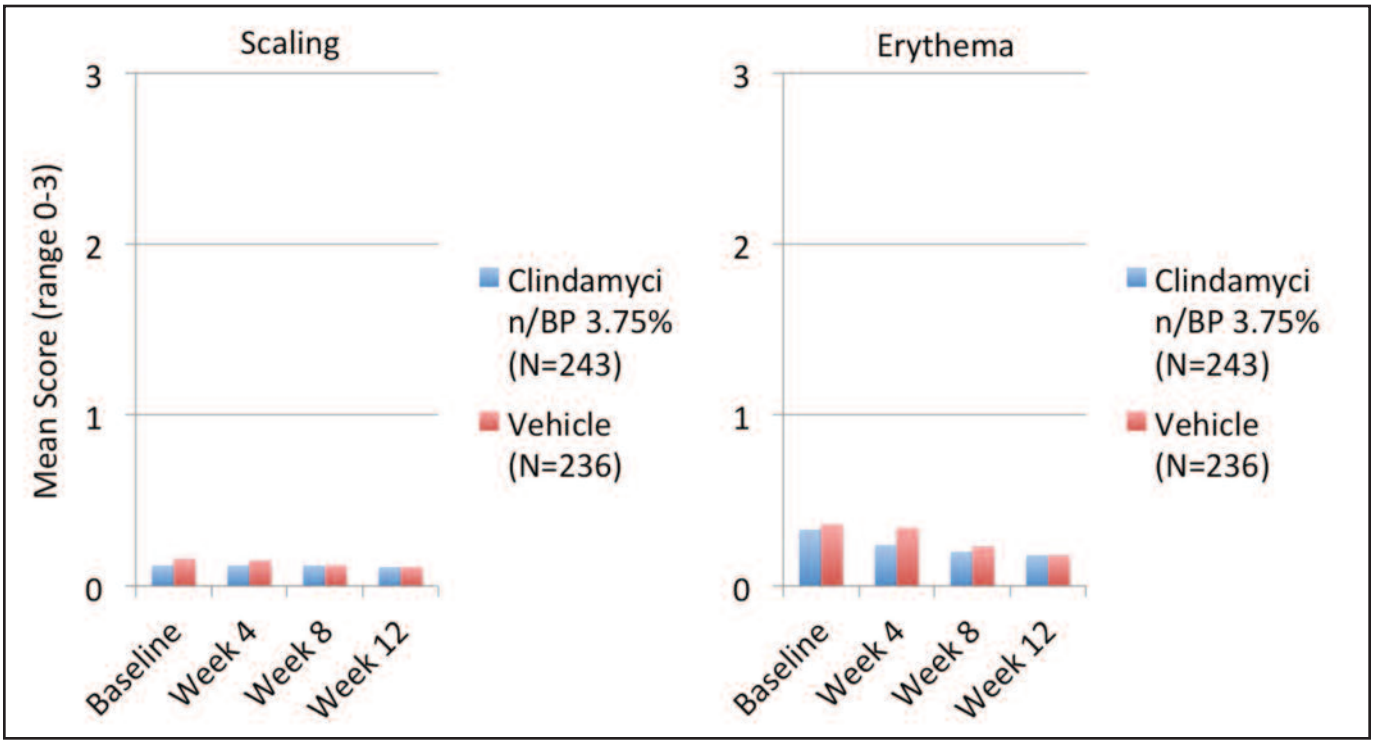

Figure 1. Investigator assessment of cutaneous safety (baseline to Week 12), mean scores/safety population

(Table 1). Maximum post-baseline scores reported were the highest level of severity noted for each parameter after the baseline visit.

Statistical analysis. The safety population comprised all randomized patients who were presumed to have used the study medication at least once and who provided at least one post-baseline evaluation.

Frequencies and percentages for each outcome category were included in the statistics and mean values calculated by week and by study drug group.

RESULTS

Investigator assessment of cutaneous safety. Overall, there were no reports of erythema or scaling at any post-baseline study visit in more than 80 percent of patients in the clindamycin phosphate 1.2%/BP 3.75% group (80 and 88%, respectively) and more than 71 percent in the vehicle group (71 and 86%, respectively). In both cases, reports of erythema or scaling reduced from Week 4 to the end of study (Week 12).

Mean scores for erythema and scaling were low throughout the study, reducing over its duration, and again similar between active and vehicle. At Week 4, mean erythema and scaling scores with clindamycin phosphate 1.2%/BP 3.75% were 0.24 (±0.52) and 0.12 (±0.37), respectively, reducing to 0.18 (±0.43) and 0.11 (±0.32), respectively, at Week 12 (Figure 1).

When they did occur, the majority of cases of erythema and scaling were mild (i.e., with slight pink coloration or barely perceptible with fine scales present on limited areas of the face). There were eight reports (3.3%) of moderate erythema and four reports (1.7%) of moderate scaling at Week 4 (Table 2). In both cases, the reported incidence dropped markedly throughout the study. There was one report (0.4%) of severe erythema at Week 4 (in a post-adolescent female) (Table 3).

A *post hoc* analysis of cutaneous safety assessments stratified by age and gender was conducted. The incidence of reported mild erythema was lower in the younger females (<18 years old) and older males (≥18 years old), and in the former group there were no reports of moderate erythema (Table 3). The incidence of reported mild scaling was lower in the younger patients (<18 years old) (Table 4).

Although severe erythema and scaling were reported on two occasions (one each) at baseline, there were no reports of severe erythema or scaling while patients were treated with vehicle.

Patient assessment of cutaneous tolerability. Overall, reports of itching, burning or stinging were rare at any post-baseline study visit, not being seen at all in more than 87 percent of patients in the clindamycin phosphate 1.2%/BP 3.75% group (range 87–95%), and 86 percent of patients in the vehicle group (range 86–97%). Tolerability also improved from Week 4 to end of study (Week 12).

Mean scores for itching, burning, and stinging were low throughout the study, reducing over its duration, and again similar between active and vehicle. At Week 4, mean itching, burning, and stinging scores with clindamycin phosphate 1.2%/BP 3.75% were 0.14 (±0.49), 0.06 (±0.30), and 0.04 (±0.20), respectively, reducing to 0.10

(±0.36), 0.03 (±0.20), and staying constant at 0.04 (±0.26), respectively, at Week 12 (Figure 2).

When they did occur, the majority of cases of itching, burning, and stinging were mild (i.e., slight itching, burning or stinging sensation, not really bothersome). There were three reports (1.2%) of moderate itching, one report of moderate burning (0.4%), and no reports of moderate stinging at Week 4. Incidences of moderate itching, burning, and stinging stayed constant throughout the study (Table 5). There was one report (0.4%) of severe burning (at Week 4 in an adolescent female, Table 5) and one report (0.4%) of severe stinging (Week 12 in an adolescent male, Table 5).

A *post hoc* analysis of cutaneous tolerability assessments stratified by age and gender was conducted. The incidence of reported mild itching and burning was lower in the younger patients (<18 years old). Mild stinging tended to be similar across all age and gender groups.

There were two reports (0.8%) of severe itching at baseline with vehicle that resolved by Week 12.

DISCUSSION

Both patient surveys[10] and clinical data[8] have supported the view that cutaneous safety and tolerability of topical acne treatments have an important impact on how patients take their medication and is likely to significantly affect outcomes. The use of fixed combinations where both active ingredients are potentially irritating has exacerbated the problem, although advances in formulation research have started to provide dermatology with options that are both safe and efficacious.

Clindamycin phosphate 1.2%/BP 3.75% is a new fixed combination treatment for moderate-to-severe acne vulgaris. Results from the pivotal Phase 3 trial showed it to be generally safe and well-tolerated.[13] Treatment-emergent adverse events (TEAEs) occurred in fewer than two percent of patients (compared with 3.0% with vehicle).[13] There were no discontinuations because of TEAEs.[13]

Although the overall good cutaneous tolerability and safety of clindamycin phosphate 1.2%/BP 3.75% has been previously reported, no specific data on outliers have been provided.

For most patients treated with

TABLE 2. Summary of investigator assessment of cutaneous safety (baseline to Week 12 and maximum post-baseline)

	BASELINE	WEEK 4	WEEK 8	WEEK 12	MAXIMUM POST-BASELINE
ERYTHEMA					
Clindamycin/BP 3.75%					
0=None	179 (73.7%)	194 (80.5%)	196 (82.0%)	197 (83.8%)	164 (67.5%)
1=Mild	49 (20.2%)	38 (15.8%)	38 (15.9%)	34 (14.5%)	67 (27.6%)
2=Moderate	15 (6.2%)	8 (3.3%)	5 (2.1%)	4 (1.7%)	11 (4.5%)
3=Severe	0	1 (0.4%)	0	0	1 (0.4%)
Not reported	0	2	4	8	0
Vehicle					
0=None	172 (72.9%)	167 (71.1%)	174 (79.1%)	178 (83.6%)	150 (63.6%)
1=Mild	45 (19.1%)	56 (23.8%)	41 (18.6%)	31 (14.6%)	69 (29.2%)
2=Moderate	18 (7.6%)	12 (5.1%)	5 (2.3%)	4 (1.9%)	17 (7.2%)
3=Severe	1 (0.4%)	0	0	0	0
Not reported	0	1	16	23	0
SCALING					
Clindamycin/BP 3.75%					
0=None	217 (89.3%)	216 (89.6%)	212 (88.7%)	211 (89.8%)	191 (78.6%)
1=Mild	23 (9.5%)	21 (8.7%)	25 (10.5%)	23 (9.8%)	45 (18.5%)
2=Moderate	3 (1.2%)	4 (1.7%)	2 (0.8%)	1 (0.4%)	7 (2.9%)
3=Severe	0	0	0	0	0
Not reported	0	2	4	8	0
Vehicle					
0=None	206 (87.3%)	202 (86.0%)	190 (86.4%)	195 (91.5%)	180 (76.3%)
1=Mild	25 (10.6%)	31 (13.2%)	29 (13.2%)	16 (7.5%)	51 (21.6%)
2=Moderate	3 (1.3%)	2 (0.9%)	1 (0.5%)	1 (0.9%)	5 (2.1%)
3=Severe	2 (0.8%)	0	0	0	0
Not reported	0	1	16	23	0

TABLE 3. Incidence and severity of erythema by gender and age with clindamycin/BP 3.75%

	BASELINE	WEEK 4	WEEK 8	WEEK 12	MAXIMUM POST-BASELINE
MALES (<18)					
1=Mild	19	17	18	17	34
2=Moderate	6	3	2	1	4
3=Severe	0	0	0	0	0
Not reported	0	0	0	1	0
MALES (≥18)					
1=Mild	8	3	4	3	5
2=Moderate	3	3	2	1	4
3=Severe	0	0	0	0	0
Not reported	0	1	3	3	0
FEMALES (<18)					
1=Mild	8	6	10	8	13
2=Moderate	1	0	0	0	0
3=Severe	0	0	0	0	0
Not reported	0	1	0	1	0
FEMALES (≥18)					
1=Mild	14	12	6	6	15
2=Moderate	5	2	1	2	3
3=Severe	0	1	0	0	1
Not reported	0	0	1	3	0

TABLE 4. Incidence and severity of scaling by gender and age with clindamycin/BP 3.75%

	BASELINE	WEEK 4	WEEK 8	WEEK 12	MAXIMUM POST-BASELINE
MALES (<18)					
1=Mild	11	7	12	8	17
2=Moderate	1	2	1	0	3
3=Severe	0	0	0	0	0
Not reported	0	0	0	1	0
MALES (≥18)					
1=Mild	3	3	5	4	8
2=Moderate	0	0	0	0	0
3=Severe	0	0	0	0	0
Not reported	0	1	3	3	0
FEMALES (<18)					
1=Mild	5	1	3	5	5
2=Moderate	1	1	1	1	3
3=Severe	0	0	0	0	0
Not reported	0	1	0	1	0
FEMALES (≥18)					
1=Mild	4	10	5	6	15
2=Moderate	1	1	0	0	1
3=Severe	0	0	0	0	0
Not reported	0	0	1	3	0

clindamycin phosphate 1.2%/BP 3.75%, no local signs and symptoms of erythema, scaling, itching, burning or stinging were reported. On the rare occasions when they did occur, the vast majority were mild, not bothersome; and usually occurred early in the study, disappearing by Week 12.

Severe reactions to clindamycin phosphate 1.2%/BP 3.75% were very rare, with only three reports. There was one report of severe erythema (0.4%) in a post-adolescent female patient, one report of severe burning (0.4%) in an adolescent girl, and one report of severe stinging (0.4%) in

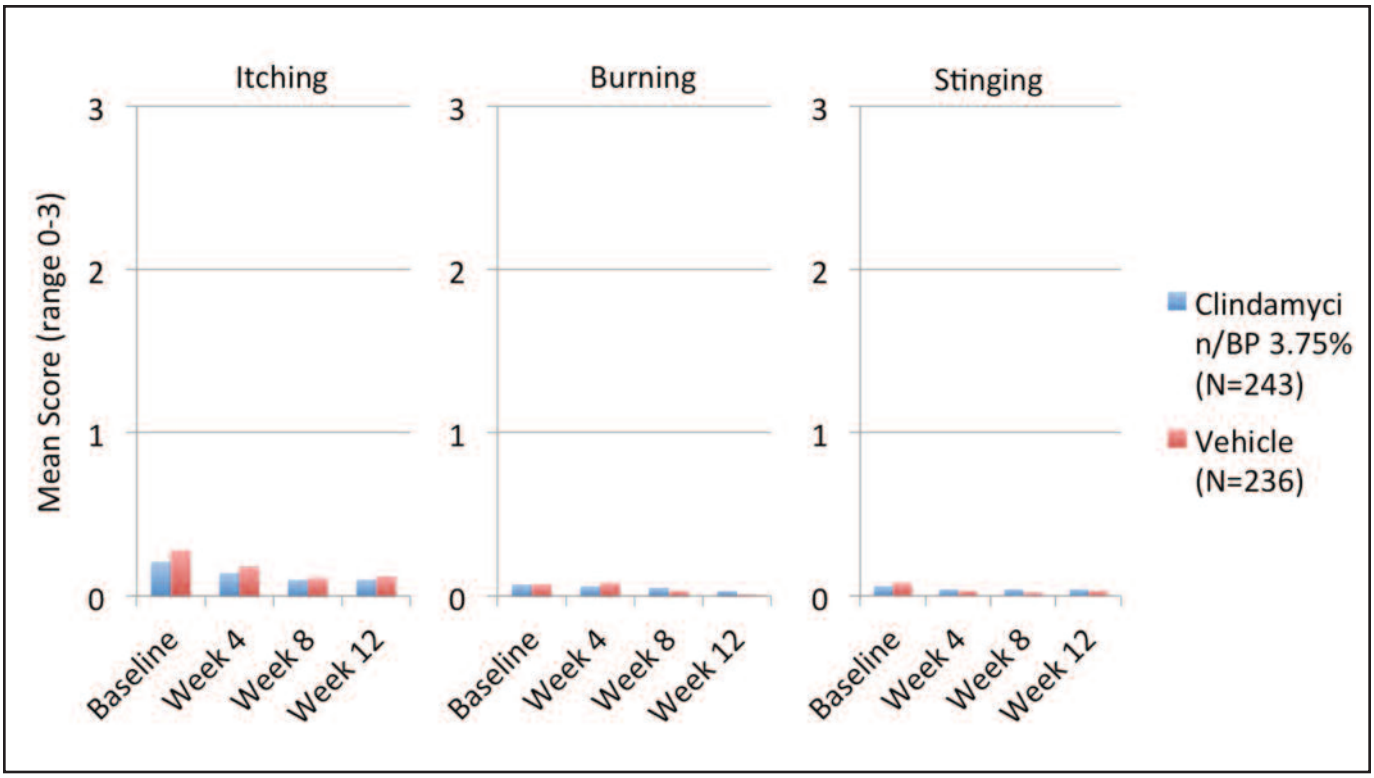

Figure 2. Patient assessment of cutaneous tolerability (baseline to Week 12), mean scores/safety population

an adolescent boy. Two of these resolved over the course of treatment, with one (stinging) only being reported at study end. The incidence of severe local signs and symptoms was similar to that seen with vehicle.

There are limitations to the author's study. Given the similar results seen overall with clindamycin phosphate 1.2%/BP 3.75% and vehicle, it is not possible to determine whether any of the severe reactions reported were due to active or vehicle. In addition, although the *post hoc* analysis looks at age and gender, no information on acne severity was available.

The good safety and tolerability profile of clindamycin phosphate 1.2%/BP 3.75% in treating moderate-to-severe acne has already been reported.[13] The author's analysis of outlier data further confirms these findings.

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TABLE 5. Summary of patient assessment of cutaneous tolerability (baseline to Week 12 and maximum post-baseline)

	BASELINE	WEEK 4	WEEK 8	WEEK 12	MAXIMUM POST-BASELINE
ITCHING					
Clindamycin/BP 3.75%					
0=None	201 (82.7%)	210 (87.1%)	219 (91.6%)	215 (91.5%)	198 (81.5%)
1=Mild	35 (14.4%)	28 (11.6%)	17 (7.1%)	16 (6.8%)	37 (15.2%)
2=Moderate	6 (2.5%)	3 (1.2%)	3 (1.3%)	4 (1.7%)	8 (3.3%)
3=Severe	1 (0.4%)	0	0	0	0
Not reported	0	2	4	8	0
Vehicle					
0=None	185 (78.4%)	203 (86.4%)	199 (90.5%)	192 (90.1%)	186 (78.8%)
1=Mild	38 (16.1%)	24 (10.2%)	18 (8.2%)	17 (8.0%)	36 (15.3%)
2=Moderate	11 (4.7%)	6 (2.6%)	2 (0.9%)	4 (1.9%)	12 (5.1%)
3=Severe	2 (0.8%)	2 (0.9%)	1 (0.5%)	0	2 (0.8%)
Not reported	0	1	16	23	0

TABLE 5 continued. Summary of patient assessment of cutaneous tolerability (baseline to Week 12 and maximum post-baseline)

	BASELINE	WEEK 4	WEEK 8	WEEK 12	MAXIMUM POST-BASELINE
BURNING					
Clindamycin/BP 3.75%					
0=None	230 (94.7%)	229 (95.0%)	229 (95.8%)	228 (97.0%)	221 (90.9%)
1=Mild	11 (4.5%)	10 (4.1%)	8 (3.3%)	6 (2.6%)	18 (7.4%)
2=Moderate	1 (0.4%)	1 (0.4%)	2 (0.8%)	1 (0.4%)	3 (1.2%)
3=Severe	1 (0.4%)	1 (0.4%)	0	0	1 (0.4%)
Not reported	0	2	4	8	0
Vehicle					
0=None	223 (94.5%)	221 (94.0%)	214 (97.3%)	211 (99.1%)	219 (92.8%)
1=Mild	10 (4.2%)	10 (4.3%)	5 (2.3%)	2 (0.9%)	11 (4.7%)
2=Moderate	3 (1.3%)	4 (1.7%)	1 (0.5%)	0	6 (2.5%)
3=Severe	0	0	0	0	0
Not reported	0	1	16	23	0
STINGING					
Clindamycin/BP 3.75%					
0=None	229 (94.2%)	231 (95.9%)	230 (96.2%)	227 (96.6%)	225 (92.6%)
1=Mild	13 (5.3%)	10 (4.1%)	9 (3.8%)	7 (3.0%)	17 (7.0%)
2=Moderate	1 (0.4%)	0	0	0	0
3=Severe	0	0	0	1 (0.4%)	1 (0.4%)
Not reported	0	2	4	8	0
Vehicle					
0=None	220 (93.2%)	229 (97.4%)	216 (98.2%)	208 (97.7%)	221 (93.6%)
1=Mild	12 (5.1%)	6 (2.6%)	3 (1.4%)	4 (1.9%)	13 (5.5%)
2=Moderate	4 (1.7%)	0	1 (0.5%)	1 (0.5%)	2 (0.8%)
3=Severe	0	0	0	0	0
Not reported	0	1	16	23	0

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